Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection

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What to Start: Regimens Recommended for Initial Therapy of Antiretroviral-Naive Children (Last updated April 26, 2016; last reviewed April 26, 2016)

Panel's Recommendations
• Selection of an initial regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing **(AIII)**.
• For treatment-naive children, the Panel recommends initiating antiretroviral therapy with three drugs, including either a boosted protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor plus a dual-nucleoside/nucleotide reverse transcriptase inhibitor backbone.
• Table 7 provides a list of Panel-recommended regimens that are "Preferred," "Alternative" or for "Use in Special Circumstances;" recommendations vary by age, weight, and sexual maturity rating.
• For infants aged <42 weeks postmenstrual or <14 days postnatal, data are currently inadequate to provide recommended dosing to allow the formulation of an effective, complete antiretroviral therapy regimen (see Specific Issues in Antiretroviral Therapy in Newborn Infants with HIV Infection).
• Emtricitabine, lamivudine, and tenofovir disoproxil fumarate have antiviral activity and efficacy against hepatitis B. For a comprehensive review of this topic, and hepatitis C and tuberculosis during HIV coinfection, the reader should access the Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Exposed and HIV-Infected Children.
Rating of Recommendations: *A = Strong; B = Moderate; C = Optional*
Rating of Evidence: *I = One or more randomized trials in children† with clinical outcomes and/or validated endpoints; I* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children† from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children† with long-term outcomes; II* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children† from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion*
† Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

Criteria Used for Recommendations

In general, the Panel on Antiretroviral Therapy and Medical Management of HIV-Infected Children (the Panel)'s recommendations are based on reviews of pediatric and adult clinical trial data published in peer-reviewed journals, data prepared by manufacturers for Food and Drug Administration (FDA) review, and data presented in abstract format at major scientific meetings. Few randomized, Phase III clinical trials of antiretroviral therapy (ART) in pediatric patients exist that provide direct comparison of different treatment regimens. Most pediatric drug data come from Phase I/II safety and pharmacokinetic (PK) trials and non-randomized, open-label studies. In general, even in adult studies, assessment of drug efficacy and potency is primarily based on surrogate marker endpoints, such as CD4 T lymphocyte (CD4) cell count and HIV RNA levels. The Panel continually modifies recommendations on optimal initial therapy for children as new data become available, new therapies or drug formulations are developed, and additional toxicities are recognized.

Information considered by the Panel for recommending specific drugs or regimens includes:

- Data demonstrating durable viral suppression, immunologic improvement, and clinical improvement (when such data are available) with the regimen, preferably in children as well as adults;
- The extent of pediatric experience with the particular drug or regimen;
- Incidence and types of short- and long-term drug toxicity with the regimen, with special attention to toxicity reported in children;
- Availability and acceptability of formulations appropriate for pediatric use, including palatability, ease of preparation (e.g., powders), volume of syrups, and pill size/number of pills;

- Dosing frequency and food and fluid requirements; and
- Potential for drug interactions with other medications.

The Panel classifies recommended drugs or drug combinations into one of several categories as follows:

- *Preferred:* Drugs or drug combinations are designated as *Preferred* for use in treatment-naive children when clinical trial data in children or, more often, in adults have demonstrated optimal and durable efficacy with acceptable toxicity and ease of use, and pediatric studies using surrogate markers demonstrate safety and efficacy; additional considerations are listed above.
- *Alternative:* Drugs or drug combinations are designated as *Alternatives* for initial therapy when clinical trial data in children or adults show efficacy but there are disadvantages compared with preferred regimens in terms of more limited experience in children; the extent of antiviral efficacy or durability is less well defined in children or less than a preferred regimen in adults; there are specific toxicity concerns; or there are dosing, formulation, administration, or interaction issues for that drug or regimen.
- *Use in Special Circumstances:* Some drugs or drug combinations are recommended for use as initial therapy only in *Special Circumstances* when preferred or alternative drugs cannot be used.

Factors to Consider When Selecting an Initial Regimen

An ART regimen for children should generally consist of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) plus one active drug from the following classes: non-nucleoside reverse transcriptase inhibitor (NNRTI), protease inhibitor (PI) boosted with ritonavir, or integrase strand transfer inhibitor (INSTI). Choice of a regimen should be individualized based on a number of factors including characteristics of the proposed regimen, patient characteristics, and results of viral resistance testing. Advantages and disadvantages of each class-based regimen are delineated in detail in the sections that follow and in Table 8. In addition, because ART will most likely need to be administered lifelong, considerations related to the choice of initial antiretroviral (ARV) regimen should also include an understanding of barriers to adherence, including the complexity of schedules and food requirements for different regimens, differing formulations, palatability problems, and potential limitations in subsequent treatment options, should resistance develop. Treatment should only be initiated after assessment and counseling of caregivers about adherence to therapy.

Choosing Among an Integrase Strand Transfer Inhibitor-Based, a Non-Nucleoside Reverse Transcriptase Inhibitor-Based, or a Boosted Protease Inhibitor-Based Initial Regimen

Preferred regimens for initial therapy include INSTI-, NNRTI-, or boosted PI-based regimens. The choice of regimen should be based on patient characteristics, especially age, results of viral drug resistance testing, drug efficacy and adverse events (AEs), patient and family preference, pill size, and dosing frequency.

Clinical trial data in children provide some guidance for choosing between an NNRTI-based regimen and a PI-based regimen for initial therapy. Three pediatric studies have compared an NNRTI-based regimen to a PI-based regimen and results varied based on age of the population studied and specific drug within the class.

- The P1060 study demonstrated superiority of a lopinavir/ritonavir (LPV/r)-based regimen compared to a nevirapine-based regimen in HIV-infected infants and children aged 2 months to 35 months, regardless of prior maternal or infant exposure to peripartum single-dose nevirapine prophylaxis (21.7% vs. 39.6% death, virologic failure, or toxicity by Week 24 with prior nevirapine exposure and 18.4% vs. 40.1% with no prior exposure).[1]
- Those in the nevirapine group demonstrated greater, but not statistically significant, improvements in immunologic status and growth. Similar improved immune and growth parameters were also demonstrated in the NEVEREST study where children switched to a nevirapine regimen versus those who continued on a rito LPV/r regimen after achieving virologic control.[2]

- PENPACT-1 (PENTA 9/PACTG 390) compared a PI-based regimen and a NNRTI-based regimen in HIV-infected treatment-naive children aged 30 days to <18 years (the study did not dictate the specific NNRTI or PI initiated). In the PI-based group, 49% of children received LPV/r and 48% received nelfinavir; in the NNRTI-based group, 61% of children received efavirenz and 38% received nevirapine. After 4 years of follow-up, 73% of children randomized to PI-based therapy and 70% randomized to NNRTI-based therapy remained on their initial ART regimen. In both groups, 82% of children had viral loads <400 copies/mL.[3]
- The PROMOTE-pediatrics trial demonstrated comparable virologic efficacy among children randomized to receive either an NNRTI or LPV/r-based ART.[4] Children were aged 2 months to <6 years and had no perinatal exposure to nevirapine. Selection of NNRTI was based on age (children aged <3 years received nevirapine and those aged >3 years primarily received efavirenz). At 48 weeks, the proportion with HIV RNA level <400 copies/mL at 48 weeks was 80% in the ritona LPV/r arm versus 76% in the NNRTI arm, a difference of 4% and not statistically significant (95% CI: -9% to +17%).

Clinical investigation of INSTI-based regimens in children has been limited to non-comparative studies demonstrating safety, tolerability, and PKs. The recommendation for an INSTI as part of an initial regimen is based largely on efficacy, tolerability and fewer drug-drug interactions in adult comparative trials showing superiority of INSTI-containing compared to PI-containing and NNRTI-containing regimens[5-7] and small studies in ART-naive adolescents.[8]

Based on the above data, the Panel considers the following as Recommended for children when used in combination with two NRTIs:

- <2 years: LPV/r
- ≥2 years to <3 years: LPV/r or raltegravir
- ≥3 to 12 years: efavirenz, raltegravir, boosted atazanavir, or twice-daily boosted darunavir
- ≥12 years who have not reached sexual maturity: dolutegravir, elvitegravir/cobicistat (only the elvitegravir/cobicistat-containing fixed drug combination elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (TAF) (i.e., Genvoya) is recommended at this time), boosted atazanavir, or once-daily boosted darunavir

Alternative regimens are shown in Table 7.

Integrase Strand Transfer Inhibitor-Based Regimens (Integrase Strand Transfer Inhibitor plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary: Integrase Strand Transfer Inhibitor-Based Regimens

Three INSTIs—dolutegravir, elvitegravir and raltegravir—are licensed for the treatment of ARV-naive HIV-infected adults. These agents have quickly become the preferred regimen in adults because of their virologic efficacy, lack of drug-drug interactions and favorable toxicity profile. Raltegravir is licensed for treatment of HIV-infected children as young as age 4 weeks. Dolutegravir is approved for use in adolescents aged ≥12 years and studies in younger children are under way. Elvitegravir has been studied in adolescents in two, fixed-dose combination regimens and in combination with two NRTIs and ritonavir boosting. At this time, only one fixed-dose combination has sufficient experience in adolescents to recommend (Table 8 lists the advantages and disadvantages of INSTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug).

Dolutegravir

The FDA has approved dolutegravir for use in children aged ≥12 years and weighing ≥40 kg. The approval was supported by data from a study of 23 treatment-experienced—but INSTI-naive—adolescents.[8] The drug has a very favorable safety profile and can be dosed once daily in treatment of INSTI-naive patients.

Efficacy in Clinical Trials:

- Dolutegravir was non-inferior to raltegravir for viral suppression to <50 copies/mL. Both were administered with two NRTI combinations in the SPRING-2 trial.[5]
- When dolutegravir in combination with abacavir and lamivudine was compared to efavirenz combined with tenofovir disoproxil fumarate (TDF) and emtricitabine, dolutegravir was superior to the efavirenz combination at week 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[7,9]
- Similar findings were noted when a dolutegravir ART regimen was compared to a darunavir/ritonavir (DRV/r) ART regimen in the FLAMINGO study. The dolutegravir regimen was found to be superior at weeks 48 and 96, mostly due to drug discontinuation in the DRV/r study arm.[6,10]
- Twenty-three adolescents were enrolled and 22 (96%) completed the 48-week study visit of a safety, pharmacokinetics and efficacy study of dolutegravir in combination with two NRTIs. Dolutegravir was administered at weight-based fixed dosages of approximately 1 mg/kg. PK parameters were within the study targets based on adult PK ranges. At week 48, 74% (95% CI: 52% to 90%) had HIV RNA <400 copies/mL and 61% (95% CI: 39% to 80%) had levels <50 copies/mL. Dolutegravir was well tolerated.[8]

Adverse Events:

- Dolutegravir is well tolerated in adults and adolescents. In adult trials, insomnia and headache were the only AEs reported with an incidence of ≥2%. In the small number of adolescents studied, there were no reported AEs attributed to dolutegravir.[8]

Other Factors and Considerations:

- There are few drug interactions with dolutegravir.
- Dolutegravir is dosed once daily and is available in a single-tablet regimen.

Recommendations:

- Based on virologic potency and safety profile in adult and pediatric studies, the Panel recommends dolutegravir in combination with a two-NRTI backbone as a **Preferred INSTI** regimen for **adolescents aged ≥12 years and weighing ≥40 kg (AI*)**.

Elvitegravir

Elvitegravir is an INSTI available as a tablet, as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TDF (Stribild), and as a fixed-dose combination tablet containing elvitegravir/cobicistat/emtricitabine/TAF. Both are FDA-approved for use as ART in HIV-1-infected ART-naive adults. Elvitegravir/cobicistat/emtricitabine/TAF is FDA-approved for use in ART-naive adolescents aged ≥12 years and weighing ≥35 kg. Cobicistat is a specific, potent cytochrome P3A (CYP3A) inhibitor that has no activity against HIV and is used as a PK enhancer, which allows for once-daily dosing of elvitegravir.

Efficacy in Clinical Trials:

- At 144 weeks, a combination of elvitegravir/cobicistat/emtricitabine/TDF was found to be non-inferior to a regimen of efavirenz/emtricitabineTDF[11] and to a regimen of atazanavir/ritonavir (ATV/r) with emtricitabine/TDF.[12]
- 1,733 adults (in 2 studies) were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TDF or elvitegravir/cobicistat/emtricitabine/TDF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; $P < 0.0001$), significantly less proteinuria (median percent change −3% vs 20%; $P < 0.0001$), and a significantly smaller decrease in bone mineral density (BMD) at spine (mean % change −1.30 vs. –2.86; $P < 0.0001$) and hip (−0.66 vs. –2.95; $P < 0.0001$).[13]

- In a small study (14 participants) of elvitegravir/cobicistat/emtricitabine/TDF in treatment-naive adolescents (aged 12 to 17 years) therapy was well tolerated, steady state exposure was similar to adults and at 24 weeks, all subjects had viral loads <400 copies/mL and 11 had viral loads <50 copies/mL.[14]
- Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive adolescents aged ≥12 years and weighing ≥35 kg and demonstrated similar PK parameters of the combination in adults, was well-tolerated and, at week 24, all subjects had viral loads <50 copies/mL.[15]

Adverse Events:

- In adult and adolescents, the most common AEs were diarrhea, nausea, and upper respiratory infection.[11,12,14,15]

Other Factors and Considerations:

- Because cobicistat inhibits CYP3A, drug-drug interactions may occur.
- Cobicistat inhibits the tubular secretion of creatinine resulting in a higher serum creatinine and a reduced estimated creatinine clearance without reducing glomerular function.
- Elvitegravir is dosed once daily.
- Elvitegravir tablets must be taken in combination with a ritonavir-boosted PI.

Recommendations:

- Based on virologic potency and safety profile in adult and adolescent studies, the Panel recommends elvitegravir only in the fixed dose combination elvitegravir/cobicistat/emtricitabine/TAF as a **Preferred INSTI** regimen for **adolescents aged ≥12 years and weighing ≥35 kg (AI*)**.

Raltegravir

Raltegravir is FDA-approved for treatment of HIV-infected children aged ≥4 weeks and weighing ≥3 kg. It is available in film-coated tablets, chewable tablets, and single packets of granules for oral suspension.

Efficacy in Clinical Trials:

- Raltegravir has been evaluated in three large randomized clinical trials (RCTs) in adults, STARTMRK, SPRING-2, and ACTG A5257. In STARTMRK, a raltegravir-containing regimen was compared to an efavirenz-containing regimen. At 48 weeks, raltegravir was non-inferior. However, with longer follow up of 4 and 5 years, more patients discontinued efavirenz and raltegravir was found to be superior.[16-18] SPRING-2 compared raltegravir to dolutegravir and demonstrated non-inferiority of dolutegravir.[5] ACTG A5257 compared raltegravir to ATV/r and DRV/r; all regimens had equivalent virologic efficacy but raltegravir had better tolerability.[19]
- Raltegravir has been studied in infants, children and adolescents in an open-label trial, IMPAACT P1066, to evaluate PK, safety, tolerability, and efficacy. In children and adolescents (96 treated at final dose of raltegravir), aged 2 through 18 years, who were mostly drug-experienced, 79.1% of the patients achieved a favorable viral load (HIV viral load <400 copies/mL or ≥1 $\log_{10}$ decline in viral load). Infants and toddlers aged ≥4 weeks to <2 years were also enrolled in P1066 and received treatment with raltegravir oral suspension. At weeks 24 and 48, 61% of the infants (14 of 23 infants) had an HIV viral load <400 copies/mL.[20-22]

Adverse Events:

- Raltegravir has a favorable safety profile.
- In P1066, drug-related adverse AEs included one child each with psychomotor hyperactivity and insomnia, rash, and elevated transaminases.

Other Factors and Considerations:

- Raltegravir lacks significant drug interactions.
- The availability of a tablet, chewable tablet, and powder formulations offers multiple options for administration. The tablet formulations are not interchangeable (they are not bioequivalent), and therefore, require different dosing.
- Twice-daily administration is necessary.

Recommendations:

- Based on RCTs in adults and pediatric studies, largely in ARV-experienced children and adolescents, the Panel recommends raltegravir as a **Preferred INSTI** in children **aged ≥2 years through 12 years** who are able to take either the chewable or film-coated tablets.
- At this time, there is limited information about the use of single packets of granules for oral suspension in children aged <2 years. Because of the limited data, the Panel recommends raltegravir granules as an **Alternative INSTI** in children aged **≥4 weeks to 2 years**.

Non-Nucleoside Reverse Transcriptase Inhibitor-Based Regimens (Non-Nucleoside Reverse Transcriptase Inhibitor plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary

Efavirenz (aged ≥3 months), etravirine (aged ≥6 years), nevirapine (aged ≥15 days), and rilpivirine (aged ≥12 years) have an FDA-approved pediatric indication for treatment of HIV infection. Advantages of NNRTIs as initial therapy include long half-life allowing for less frequent drug administration, lower risk of dyslipidemia and fat maldistribution compared to some agents in the PI class, and generally, compared to PIs, a lower pill burden. The major disadvantages of NNRTI drugs FDA-approved for use in children are that a single viral mutation can confer high-level drug resistance (except etravirine) and cross-resistance to other NNRTIs is common. Rare but serious and potentially life-threatening skin and hepatic toxicity can occur with all NNRTI drugs, but is most frequent with nevirapine, at least in HIV-infected adults. NNRTIs have the potential to interact with other drugs also metabolized via hepatic enzymes; however, these drug interactions are less frequent with NNRTIs than with boosted PI regimens (Table 8 lists the advantages and disadvantages of NNRTIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug).

Efavirenz

Efavirenz in combination with two NRTIs is the preferred NNRTI for initial therapy of children aged ≥3 to 12 years based on clinical trial experience in adults and children.

Efficacy in Clinical Trials:

In clinical trials in HIV-infected adults and children, efavirenz in combination with two NRTIs has been associated with excellent virologic response.

- Efavirenz-based regimens have proven virologically superior or non-inferior to a variety of regimens including those containing LPV/r, nevirapine, rilpivirine, atazanavir, elvitegravir, raltegravir, and maraviroc.[16,23-29]
- In the SINGLE trial in adults, dolutegravir in combination with abacavir and lamivudine was superior to efavirenz combined with TDF and emtricitabine at weeks 48 and 144. The differences were most likely due to more drug discontinuations in the efavirenz group.[7,9]
- Efavirenz in combination with two NRTIs or with a NRTI and a PI has been studied in HIV-infected children[30-36] with results comparable to those seen in adults.

Adverse Events:

- The major limitation of efavirenz is central nervous system (CNS) side effects including fatigue, poor sleeping patterns, vivid dreams, poor concentration, agitation, depression, and suicidal ideation. Although in most patients this toxicity is transient, in some, the symptoms may persist.
- The incidence of CNS AEs was correlated with efavirenz plasma concentrations.[37-40]
- The ENCORE1 study in adults demonstrated that a dose of 400 mg of efavirenz is associated with fewer AEs but non-inferior virologic response when compared with the recommended 600-mg dose of efavirenz in adults. Despite these findings, a reduction in efavirenz dose in adults is not recommended.[41,42]
- Rash may also occur with efavirenz treatment; it is generally mild and transient but appears to be more common in children than in adults.[34,36]

Other Factors and Considerations:

- Efavirenz capsules can be opened and sprinkled on age-appropriate food for use in children as young as age 3 months who weigh at least 3.5 kg.[43]
- Because of concerns regarding variable PK of the drug in the very young, the committee does not currently endorse its use for infants and children aged 3 months to 3 years.
- Although emerging information about the use of efavirenz in pregnancy is reassuring,[44-47] alternative regimens that do not include efavirenz should be strongly considered in adolescent females who are trying to conceive or who are not using effective and consistent contraception, because of the potential for teratogenicity with first-trimester efavirenz exposure, assuming these alternative regimens are acceptable to the provider and will not compromise the woman's health **(BIII)**.

Recommendation:

- Based on efficacy and tolerability, the Panel recommends efavirenz in combination with a two-NRTI backbone as the **Preferred NNRTI** regimen for initial therapy of HIV infection in **children aged ≥3 to 12 years (AI*)** and is recommended as an **Alternative NNRTI** regimen for those aged **≥12 years who are not sexually mature** (Sexual Maturity Rating [SMR] I–III).

Nevirapine

Nevirapine has extensive clinical and safety experience in HIV-infected children and has shown ARV efficacy in a variety of combination regimens.[1,3,4,48-52]

Efficacy in Clinical Trials:

- RCTs in adults have not demonstrated virologic inferiority for a nevirapine-based regimen compared to either efavirenz or atazanavir-based regimens.[53,54]
- Randomized clinical trials in children have demonstrated conflicting results (see Choice of NNRTI- versus PI-Based Initial Regimens). P1060 demonstrated superiority of LPV/r over nevirapine in children aged <3 years as have observational studies. PENPACT-1 and PROMOTE-pediatrics allowed nevirapine or efavirenz and showed no difference between an NNRTI-based and PI-based regimen but both enrolled older children.[1,3,4,52,55-57]

Adverse Events:

- Adult randomized clinical trials have demonstrated higher rates of toxicity and drug discontinuation in the nevirapine arms compared to efavirenz or ATV/r.[53,54]
- Symptomatic hepatic toxicity is more frequent in individuals with CD4 cell counts at nevirapine initiation (women with CD4 cell counts >250 cells/mm^3 and men with CD4 cell counts >400 cells/mm^3). Hepatic toxicity appears to be less frequent in children than in adults but was reported to occur at a

greater frequency among children with CD4 percentage ≥15% at therapy initiation.[50,51,58-60]

- The safety of substituting efavirenz for nevirapine in patients who have experienced nevirapine-associated hepatic toxicity is unknown. Efavirenz use in this situation has been well tolerated in the very limited number of patients in whom it has been reported, but that substitution should be attempted with caution.[61]

Other Factors and Considerations:

- In the United States, nevirapine is the only NNRTI available in liquid formulation.
- Nevirapine also should be used with caution in children with elevated pretreatment liver function tests.

Recommendation:

- Based on the rare occurrence of significant hypersensitivity reactions (HSRs), including Stevens-Johnson syndrome, rare but potentially life-threatening hepatitis,[62,63] and conflicting data about virologic efficacy compared to preferred regimens, the Panel recommends nevirapine in combination with a two-NRTI backbone as an **Alternative NNRTI** regimen for **children aged >14 days to < 3 years (AI)**.

Rilpivirine

Rilpivirine is currently available both as a single-agent formulation and a once daily, fixed-dose combination tablet containing emtricitabine and TDF. The single-agent formulation is approved for use in adolescents aged ≥12 years.

Efficacy in Clinical Trials:

- A rilpivirine-containing regimen has been compared to an efavirenz-containing regimen in two large clinical trials in adults, ECHO and THRIVE. In both studies, rilpivirine was demonstrated to be non-inferior to efavirenz. Subjects with pretreatment HIV viral loads ≥100,000 copies/mL receiving rilpivirine had higher rates of virologic failure compared to those receiving efavirenz. These findings resulted in licensure for initial therapy with rilpivirine only in patients with HIV viral load ≤100,000 copies/mL.[27,64-66]
- A study of rilpivirine, 25 mg daily in combination with 2 NRTIs in treatment-naive adolescents aged 12 to 18 years, demonstrated that the regimen was well tolerated over 48 weeks. Among adolescents with baseline viral loads ≤100,000 copies/mL, 86% had a virologic response at 24 weeks and 79% at 48 weeks.[67,68]

Adverse Events:

- Rilpivirine is generally well tolerated. In studies in adults, neurologic events were most common and included insomnia, headache, dizziness and abnormal dreams or nightmares. There were fewer drug discontinuations related to rilpivirine compared to efavirenz.
- Somnolence and nausea were the AEs reported to be associated with rilpivirine in the adolescent study. Five and 2 of 36 patients reported somnolence and nausea, respectively.
- Depressive disorders were also reported in 7 of 36 subjects of which 2 of 36 were of Grade 3 or 4.

Other Factors and Considerations:

- Current FDA approval for rilpivirine in the adolescent population is only for the single-drug formulation.

Recommendation:

- Based on the limited experience in adolescents and larger body of evidence in adults, the Panel recommends rilpivirine in combination with a two-NRTI backbone as an **Alternative NNRTI** regimen for **adolescents aged ≥12 years and with HIV viral load ≤ 100,000 copies/mL (AI*)**.

Protease Inhibitor-Based Regimens (Boosted Protease Inhibitors plus Two-Nucleoside Reverse Transcriptase Inhibitor Backbone)

Summary: Protease Inhibitor-Based Regimens

Advantages of PI-based regimens include excellent virologic potency and high barrier for development of drug resistance (requires multiple mutations). However, because PIs are metabolized via hepatic enzymes, the drugs have potential for multiple drug interactions. They may also be associated with metabolic complications such as dyslipidemia, fat maldistribution, and insulin resistance. Factors to consider in selecting a PI-based regimen for treatment-naive children include virologic potency, dosing frequency, pill burden, food or fluid requirements, availability of palatable pediatric formulations, drug interaction profile, toxicity profile (particularly related to metabolic complications), age of the child, and availability of data in children. (Table 8 lists the advantages and disadvantages of PIs. See Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.)

Ritonavir is a potent inhibitor of the cytochrome P450 3A4 (CYP3A4) isoenzyme and can be used in low doses as a PK booster when co-administered with some PIs, increasing drug exposure by prolonging the half-life of the boosted PI. Currently only LPV/r is available as a coformulated product. When ritonavir is used as a PI booster with other PIs, two agents must be administered. In addition, the use of ritonavir boosting increases the potential for hyperlipidemia[69] and drug-drug interactions.

Preferred and alternative PIs are presented in alphabetical order below.

Atazanavir Boosted with Ritonavir

Atazanavir is a once daily PI that was approved by the FDA in March 2008 for use in combination with a two-NRTI backbone in children aged ≥6 years. Approval was extended in 2014 for use in infants and children aged ≥3 months and weighing ≥5 kg. Atazanavir in combination with cobicistat has been approved by the FDA for use in adults. Its use in children and adolescents is under investigation but no data are currently available.

Efficacy in Clinical Trials:

- ATV/r has efficacy equivalent to efavirenz-based and LPV/r-based combination therapy when given in combination with two NRTIs in treatment-naive adults.[23,70-72] In ACTG A5257, ATV/r was compared to DRV/r or the INSTI raltegravir, each administered with a TDF/emtricitabine backbone. Although all three regimens had equal virologic efficacy, ATV/r was discontinued more frequently than the other regimens due to toxicity, most often hyperbilirubinemia or gastrointestinal (GI) complaints.[19]
- P1020 enrolled 195 HIV-infected ART-naive and ART-experienced patients aged 3 months to 21 years. Capsule and powder formulations and boosted and unboosted regimens were studied in this open-label study; targeted area under the curve (AUC)-directed dose finding. Of the 195 patients enrolled, 142 patients received atazanavir-based treatment at the final recommended dose. Among them, 58% were ART-naive. At week 48, 69.5% of the naive patients and 43.3% of the experienced patients had HIV viral loads ≤400 copies/mL.[73-75]
- Atazanavir in a powder formulation administered once daily boosted with liquid ritonavir was studied in infants and children aged ≥3 months and weighing ≥10 kg in two open-label clinical trials, PRINCE I and PRINCE II.[76] Sixty-five infants and children weighing between 10 and 25 kg were studied. Using a weight-band approach for determining dose, PK targets were met. The drug was well tolerated and among 41 naive infants and children, 27 (66%) achieved HIV RNA levels <50 copies at week 48.

Adverse Events:

- The main adverse effect associated with ATV/r is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations.

- Although atazanavir is associated with fewer lipid abnormalities than other PIs, lipid levels are higher with ritonavir boosting than with atazanavir alone.[69]

Other Factors and Considerations:

- Atazanavir is available in a powder and capsule formulations administered once daily.
- Atazanavir is not coformulated with ritonavir so liquid or tablet ritonavir must also be given.
- Atazanavir co-formulated with cobicistat is FDA-approved for adults but has not been studied in children.

Recommendations:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies, the Panel recommends atazanavir capsules boosted with ritonavir in combination with a two-NRTI backbone as a **Preferred PI regimen for children aged ≥3 years (AI*)**.
- Because of the limited experience with atazanavir boosted with ritonavir in younger children, the Panel recommends atazanavir boosted with ritonavir as **Alternative PI therapy in infants and children aged >3 months to < 3 years and weighing between 5 and 25 kg (AI*)**.
- The Panel does not recommend unboosted atazanavir.

Darunavir Boosted with Ritonavir

Darunavir boosted with ritonavir is FDA-approved for ARV-naive and ARV-experienced adults and for ARV-naive and ARV-experienced children aged ≥3 years.

Efficacy in Clinical Trials:

- In a randomized, open-label trial in adults, DRV/r (800/100 mg once daily) was compared to LPV/r (once or twice daily) when both boosted PIs were administered in combination with TDF fumarate/emtricitabine. DRV/r was found to be non-inferior at week 48 and superior at week 192. AEs were also less common in the DRV/r group ($P < 0.01$).[77,78]
- DRV/r was compared to dolutegravir, both in combination with a two-NRTI backbone, in the FLAMINGO study. The rate of virologic suppression was greater with dolutegravir mainly due to more drug discontinuation in the DRV/r treatment arm.[10]
- ART with DRV/r, ATV/r and raltegravir showed similar virologic suppression in the ACTG A5257 study.[19]
- To date the only clinical trial of darunavir boosted with ritonavir as initial therapy in pediatric patients is the DIONE study of once-daily DRV/r in treatment-naive adolescents aged 12 to 18 years (mean age, 14.6 years). After 24 weeks of treatment, 11 of 12 subjects had HIV-1 RNA <50 copies/mL and the agents were well tolerated.[79]
- In a study of treatment-experienced children (aged 6–17 years), DELPHI, twice daily DRV/r-based therapy was well tolerated and 48% of the children achieved HIV-1 RNA <50 copies/mL by 48 weeks.[80]
- In a study of treatment-experienced pediatric participants (aged 3 to <6 years and weighing ≥10 kg to <20 kg), ARIEL, 57% of subjects had HIV-1 RNA <50 copies/mL and 81% < 400 copies/mL after 24 weeks of treatment with twice daily DRV/r.[81]

Adverse Events:

- DRV/r is generally well tolerated in children and adolescents with the most commonly reported AEs being vomiting, diarrhea, abdominal pain, rash and headache.

Other Factors and Considerations:

- Darunavir is available as an oral suspension and tablet.

- Because of available pill sizes and twice-daily administration in young children, regimens may be complicated by multiple pills and different pill strengths.
- DRV/r is approved for once-daily use in adults and children. A PK study of 24 patients, aged 14 to 23 years receiving once-daily DRV/r demonstrated darunavir exposure similar to that in adults receiving once-daily therapy. There was, however, a trend toward lower exposures in those aged <18 years.[82]
- In the ARIEL study, 10 treatment-experienced children were switched from twice-daily dosing to once-daily dosing after 24 weeks of therapy. PK studies were performed after 2 weeks of once-daily dosing and demonstrated darunavir mean AUC 24-hour equivalent to 128% of the adult AUC 24 hour.[83]

Recommendations:

- Based on its virologic potency in adult and pediatric studies, high barrier to development of drug resistance, and excellent toxicity profile in adults and children, the Panel recommends darunavir boosted with ritonavir in combination with a two-NRTI backbone as a **Preferred PI regimen for children aged ≥3 years and adolescents (AI*)**.
  - **Once-daily dosing** of DRV/r is part of a **Preferred PI regimen in treatment-naive adolescents aged >12 years (AI*)** based on findings from the DIONE study.
  - **Twice daily dosing** of DRV/r is part of a **Preferred PI regimen in children aged ≥3 to <12 years (AI*)**.
  - **Twice daily dosing** of DRV/r if the following darunavir resistance-associated substitutions are present in the HIV protease: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

Lopinavir Boosted with Ritonavir

Lopinavir boosted with ritonavir is approved for treatment of HIV infection in adults and in infants and children with a postmenstrual age ≥42 weeks and postnatal age ≥14 days.

Efficacy in Clinical Trials:

- In clinical trials of treatment-naive adults, regimens containing LPV/r plus two NRTIs have been demonstrated to be comparable to a variety of other regimens including atazanavir, darunavir (at 48 weeks), fosamprenavir, saquinavir/ritonavir, and efavirenz, superior to nelfinavir, and inferior to darunavir (at 192 weeks).[25,70,72,77,84-88]
- LPV/r has been studied in both ARV-naive and ARV-experienced children and has demonstrated durable virologic activity and low toxicity.[52,89-95]

Adverse Events:

- In adults, LPV/r is associated with diarrhea, insulin resistance, and hyperlipidemia. These adverse events may be exacerbated by the higher dose of ritonavir used for boosting with lopinavir (200 mg) compared to atazanavir and darunavir (100 mg).
- Post-marketing reports of LPV/r-associated cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, CNS depression, and respiratory complications leading to death have been reported, predominantly in preterm neonates. These reports have resulted in a change in LPV/r labeling including a recommendation to not administer the combination to neonates until they reach a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.

Other Factors and Considerations:

- LPV/r is available coformulated as a capsule and an oral solution.
- Dosing and efficacy data are available in infants as young as age 25 days.[93,96]
- Once-daily LPV/r is FDA-approved for initial therapy in adults,[97] but PK data in children do not support a recommendation for once-daily dosing.[98-100]

Recommendations:

- Based on virologic potency in adult and pediatric studies and tolerability in pediatric studies, the Panel recommends LPV/r in combination with a two-NRTI backbone as a **Preferred PI regimen for infants with a postmenstrual age ≥42 weeks and postnatal age ≥14 days to <12 years (AI)**.

Selection of Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone as Part of Initial Combination Therapy

Summary: Selection of Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone Regimen

Dual-NRTI combinations form the backbone of combination regimens for both adults and children. Currently, seven NRTIs (zidovudine, didanosine, lamivudine, stavudine, abacavir, emtricitabine, and TDF) are FDA-approved for use in children aged <13 years. Dual-NRTI combinations that have been studied in children include zidovudine in combination with abacavir, didanosine, or lamivudine; abacavir in combination with lamivudine, stavudine, or didanosine; emtricitabine in combination with stavudine or didanosine; and TDF in combination with lamivudine or emtricitabine.[32,73,101-105] Advantages and disadvantages of different dual-NRTI backbone options are delineated in Table 8. Also, see Appendix A: Pediatric Antiretroviral Drug Information for detailed pediatric information on each drug.

In the dual-NRTI regimens listed below, lamivudine and emtricitabine are interchangeable. Both lamivudine and emtricitabine are well tolerated with few AEs. Although there is less experience in children with emtricitabine than with lamivudine, it is similar to lamivudine and can be substituted for lamivudine as one component of a preferred dual-NRTI backbone (i.e., emtricitabine in combination with abacavir or TDF or zidovudine). The main advantage of emtricitabine over lamivudine is that it can be administered once daily as part of an initial regimen. Both lamivudine and emtricitabine select for the M184V resistance mutation, which is associated with high-level resistance to both drugs; a modest decrease in susceptibility to abacavir and didanosine, and improved susceptibility to zidovudine, stavudine, and TDF based on decreased viral fitness.[106,107]

Dual-Nucleoside Reverse Transcriptase Inhibitor Backbone Regimens (in Alphabetical Order)

Abacavir in Combination with Lamivudine or Emtricitabine

Abacavir is approved for use in children aged ≥3 months when administered as part of an ART regimen.

Efficacy in Clinical Trials:

- Abacavir in combination with lamivudine has been shown to be as potent as or possibly more potent than zidovudine in combination with lamivudine in both children and adults.[108,109]
- Abacavir in combination with lamivudine has been compared to TDF with emtricitabine in several adult studies and meta-analyses with variable results.[110-113]
- Retrospective observational data from African children aged <16 years suggests the possibility of worse virologic outcome with abacavir/lamivudine-based first-line ART when compared to stavudine/lamivudine-based first-line ART.[114,115] Multiple confounders could have contributed to these findings and further data collection and evaluation is warranted.
- Abacavir combined with lamivudine was compared to zidovudine plus lamivudine and stavudine plus lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also contained either nevirapine or efavirenz. All NRTIs had low toxicity and good clinical, immunologic and virologic responses.[116]

Adverse Events:

- Abacavir-associated life-threatening HSRs occur in a small proportion of patients. HSRs are more common in individuals with certain HLA genotypes, particularly HLA-B*5701. Before initiating

abacavir-based therapy in HIV-infected children, genetic screening for HLA-B*5701 should be performed and children who test positive for HLA-B*5701 should not receive abacavir **(AII*)**.

Other Factors and Considerations:

- Abacavir can be administered once daily in patients who are able to tolerate pill formulation of abacavir or abacavir-containing fixed-dose combination tablets.
- Infants and young children who initiate abacavir therapy with the liquid formulation should receive twice-daily abacavir. In children with undetectable plasma RNA after approximately 24 weeks of abacavir therapy, the change to once-daily administration, with appropriate dose modification, can be made.[117-120]

Recommendations:

- Based on virologic efficacy and favorable toxicity profile, the Panel recommends abacavir plus lamivudine or emtricitabine **as the Preferred dual-NRTI** combination for **children aged ≥3 months (AI)**.
- Once-daily doing of abacavir is recommended when using the pill formulation. Twice daily dosing of liquid abacavir is recommended for initial therapy; a change to once-daily dosing can be considered, based on response, after approximately 24 weeks of dosing.

Tenofovir Alafenamide in Combination with Emtricitabine

TAF is an oral prodrug of tenofovir. It has recently been approved by the FDA as a component of the fixed-drug combination tablet also containing elvitegravir, cobicistat, and emtricitabine for the treatment of HIV infection in ARV-naive individuals aged ≥12 years with estimated creatinine clearance ≥30 mL/min.

Efficacy in Clinical Trials:

- In 2 studies, 1,733 adults were randomly assigned to receive either elvitegravir/cobicistat/emtricitabine/TAF or elvitegravir/cobicistat/emtricitabine/TDF. After 48 weeks, those receiving elvitegravir/cobicistat/emtricitabine/TAF had significantly smaller mean serum creatinine increases (0.08 vs. 0.12 mg/dL; $P < 0.0001$), significantly less proteinuria (median % change −3 vs. 20; $P < 0.0001$), and a significantly smaller decrease in BMD at the spine (mean % change −1.30 vs. –2.86; $P < 0.0001$) and hip (−0.66 vs. –2.95; $P < 0.0001$).[13]
- Elvitegravir/cobicistat/emtricitabine/TAF was studied in 49 ART-naive adolescents aged ≥12 years and weighing ≥35 kg and demonstrated PK parameters similar to those for the combination in adults, was well-tolerated and, at week 24, all subjects had viral loads <50 copies/mL.[15]

Adverse Effects:

- Compared to TDF, which readily converts to tenofovir in the plasma, TAF remains stable in the plasma resulting in lower plasma and higher intracellular concentrations of tenofovir. TAF has fewer renal and bone AEs than does TDF.
- TAF has increased serum lipid levels compared with TDF in adolescents and adults.

Other Factors and Considerations:

- TAF is only available as a component of the fixed-drug combination of elvitegravir/cobicistat/emtricitabine/TAF.
- There is limited information about the long-term efficacy and safety of TAF.

Recommendations:

- Based on the potential for less renal and bone AEs, the Panel recommends TAF plus emtricitabine (combined with elvitegravir and cobicistat) as a **Recommended dual-NRTI combination in adolescents aged ≥12 years with estimated creatinine clearance ≥30 mL/min**.

Tenofovir Disoproxil Fumarate in Combination with Lamivudine or Emtricitabine

TDF is FDA-approved for use in children and adolescents aged ≥2 years when administered as part of an ART regimen.

Efficacy in Clinical Trials:

- In comparative clinical trials in adults, TDF when used with lamivudine or emtricitabine as a dual-NRTI backbone was superior to zidovudine used with lamivudine and efavirenz in viral efficacy.[121,122]
- TDF with emtricitabine has been compared to abacavir in combination with lamivudine in several adult studies and meta-analyses with variable results.[110–113]
- TDF has been studied in HIV-infected children in combination with other NRTIs and has efficacy similar to zidovudine or stavudine.[102-105]

Adverse Effects:

- In some but not all studies, decreases in BMD have been observed in both adults and children taking TDF for 48 weeks.[102-105,123,124] The clinical significance of these changes is not yet known.
- Renal toxicity has been reported in children receiving TDF.[125-128] Numerous drug-drug interactions with TDF and other ARV drugs, including didanosine, LPV/r, atazanavir, and tipranavir, complicate appropriate dosing of TDF.

Other Factors and Considerations:

- The fixed-dose combination of TDF and emtricitabine and other available three-drug fixed-dose combination formulations containing TDF allow for once-daily dosing of a single-tablet regimen, which may help improve adherence.
- Both emtricitabine and lamivudine, and TDF have antiviral activity and efficacy against hepatitis B virus (HBV).

Recommendations:

- Based on virologic efficacy and ease of dosing, the Panel recommends TDF in combination with lamivudine or emtricitabine as an **Alternative dual-NRTI** combination for use in children and adolescents at Sexual Maturity Rating (SMR) III **(AI*)**.
- Because of decreases in BMD observed in adults and children receiving TDF and its unknown clinical significance, the Panel recommends TDF use in children aged ≥2 years and SMR I or II in **Special Circumstances** after weighing potential risks of decreased BMD versus benefits of therapy.

Zidovudine in Combination with Lamivudine or Emtricitabine

Zidovudine is available as a syrup, capsule, tablet and injectable/intravenous preparations. It is licensed for treatment in infants as young as 4 weeks and prophylaxis in newborns.

Efficacy in Clinical Trials:

- Zidovudine with lamivudine has been extensively studied in children and has been a part of ART regimens in many trials.
- Zidovudine combined with lamivudine was compared to abacavir plus lamivudine and stavudine plus lamivudine in children aged <5 years in the CHAPAS-3 study. All regimens also contained either nevirapine or efavirenz. All NRTIs had low toxicity and good clinical, immunologic, and virologic responses.[116]

Adverse Effects:

- Data on the safety of this combination in children are extensive and the combination is generally well tolerated.[129]

- Major toxicities associated with zidovudine/lamivudine are bone marrow suppression, manifested as macrocytic anemia and neutropenia, and an association with lipoatrophy; minor toxicities include GI toxicity and fatigue.
- Compared to abacavir and TDF, zidovudine is associated with greater mitochondrial toxicity.[130,131]

Other Factors and Considerations:

- Dosing information is available for newborns, including premature infants, because zidovudine has been studied extensively as an HIV prophylaxis regimen.

Recommendations:

- Because of the extensive experience and favorable safety profile, the Panel recommends zidovudine in combination with lamivudine or emtricitabine as a **Preferred NRTI** for infants and children from **birth to ≤12 years (AI*)**.
- In adolescents, the Panel recommends zidovudine in combination with lamivudine or emtricitabine as an **Alternative NRTI** because zidovudine must be administered twice daily.

Alternative Dual-Nucleoside Reverse Transcriptase Inhibitor Regimens

Other dual-NRTI regimens have been studied in children and the Panel recommends as alternative dual-NRTI combinations:

Zidovudine in Combination with Abacavir or Didanosine (BII)

- In a large pediatric study, the combination of zidovudine and didanosine had the lowest rate of toxicities.[129]
- Zidovudine/abacavir and zidovudine/lamivudine had lower rates of viral suppression and more toxicity leading to drug modification than did abacavir/lamivudine in a European pediatric study.[101,109]

Didanosine in Combination with Lamivudine or Emtricitabine (BI*)

- The combination of didanosine and emtricitabine allows for once-daily dosing.[32]
- Didanosine is recommended to be administered on an empty stomach but that is impractical for infants who must be fed frequently and it may decrease medication adherence in older children because of the complexity of the regimen.
- To improve adherence, some practitioners recommend administration of didanosine to young children without regard to timing of meals. However, data are inadequate to allow a strong recommendation at this time, and it is preferable to administer didanosine under fasting conditions when possible.

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children
(page 1 of 2)

An ART regimen in treatment-naive children generally contains one NNRTI or one PI boosted with ritonavir or one INSTI **plus** a two-NRTI backbone. Regimens should be individualized based on advantages and disadvantages of each combination (see Table 8).

For children who are receiving an effective and tolerable ART regimen, that regimen can be continued as they age even if the combination they are receiving is no longer a preferred regimen.

Preferred Regimens	
Children aged ≥14 Days to <3 Years[a]	Two NRTIs **plus** LPV/r
Children Aged ≥2 Years to <3 Years	Two NRTIs plus LPV/r
	Two NRTIs plus RAL[b]

Table 7. Antiretroviral Regimens Recommended for Initial Therapy for HIV Infection in Children
(page 2 of 2)

Preferred Regimens, continued	
Children Aged ≥3 Years to <12 Years	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** twice daily DRV/r
	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** LPV/r
	Two NRTIs **plus** RAL[b]
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** ATV/r
	Two NRTIs **plus** DTG[d]
	Two NRTIs **plus** once daily DRV/r[e]
	Two NRTIs **plus** EVG/c[f]
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative Regimens	
Children Aged >14 Days to <3 Years	Two NRTIs **plus** NVP[g]
Children Aged ≥4 Weeks and <2 Years and Weighing ≥3 kg	Two NRTIs **plus** RAL[b]
Children Aged ≥3 Months to <3 Years and Weighing ≥10 kg	Two NRTIs **plus** ATV/r
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	Two NRTIs **plus** EFV[c]
	Two NRTIs **plus** RAL[b]
	Two NRTIs **plus** RPV[h]
Preferred 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children, Birth to 3 Months	ZDV **plus** (3TC **or** FTC)
Children Aged ≥3 Months and <12 Years	ABC **plus** (3TC **or** FTC)
	ZDV **plus** (3TC **or** FTC)
Adolescents Aged ≥12 Years and Not Sexually Mature (SMR I–III)	ABC **plus** (3TC **or** FTC)
	TAF/FTC
Adolescents Aged ≥12 Years and Sexually Mature (SMR IV or V)	Refer to Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents
Alternative 2-NRTI Backbone Options for Use in Combination with Additional Drugs	
Children Aged ≥2 Weeks	ddI **plus** (3TC **or** FTC)
	ZDV **plus** ddI
Children Aged ≥3 Months	ZDV **plus** ABC
Adolescents at SMR III	TDF **plus** (3TC **or** FTC)
Adolescents Aged ≥12 Years at SMR III	ZDV **plus** (3TC **or** FTC)
2-NRTI Regimens for Use in Special Circumstances in Combination with Additional Drugs	
Children Aged ≥2 Years and Adolescents, SMR I or II	TDF **plus** (3TC **or** FTC)

[a] LPV/r should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days.

[b] RAL pills or chewable tablets can be used in children aged ≥2 years. Granules can be administered in infants and children aged 4 weeks to 2 years.

[c] EFV is licensed for use in children aged ≥3 months who weigh ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[d] DTG is recommended only for those adolescents aged ≥12 years and weighing ≥40 kg.

[e] DRV once daily should not be used in children aged <12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V.

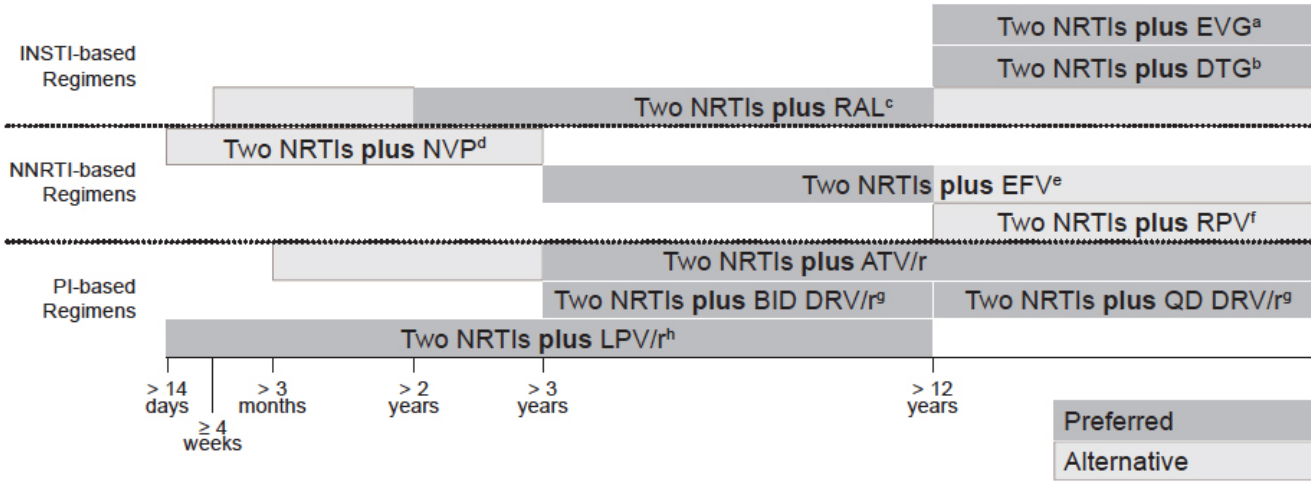
[f] EVG is currently recommended only in fixed-dose combination tablets. Tablets containing elvitegravir/cobicistat/emtricitabine/TAF are recommended as Preferred for children aged ≥12 years and weighing ≥35 kg. Tablets containing elvitegravir/cobicistat/emtricitabine/TDF are recommended only for adolescents aged ≥12 years, weighing ≥35 kg, and in SMR IV or V.

[g] NVP should not be used in post-pubertal girls with CD4 cell count >250/mm^3, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

[h] RPV should be administered to adolescents aged ≥12 years and weighing ≥35 kg who have an initial viral load ≤100,000 copies/mL.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir/ritonavir; ART = antiretroviral therapy; ddI = didanosine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; ZDV = zidovudine

Figure 1. Preferred and Alternative Regimens by Age and Drug Class



[a] EVG is currently recommended only in fixed-dose combination tablets containing elvitegravir/cobicistat/emtricitabine/TAF as Preferred for children aged ≥12 years.

[b] DTG is recommended only for children and adolescents aged ≥12 years and weighing ≥40 kg.

[c] RAL pills or chewable tablets can be used in children aged ≥2 years. Use of granules or chewable tablets in infants and children aged 4 weeks to 2 years can be considered as alternative treatment.

[d] NVP should not be used in post-pubertal girls with CD4 cell count >250/mm^3, unless the benefit clearly outweighs the risk. NVP is FDA-approved for treatment of infants aged ≥15 days.

[e] EFV is licensed for use in children aged ≥3 months and weighing ≥3.5 kg but is not recommended by the Panel as initial therapy in children aged ≥3 months to 3 years. Unless adequate contraception can be ensured, EFV-based therapy is not recommended for adolescent females who are sexually active and may become pregnant.

[f] RPV should only be used if HIV viral load is ≤100,000 copies/mL.

[g] DRV once daily should not be used in children aged <12 years and if any one of the following resistance-associated substitutions are present: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V, and L89V. Depending on weight, a combination of different strength DRV tablets to achieve the targeted dose may be required.

[h] LPV/r should not be administered to neonates before a post-menstrual age (i.e., first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and postnatal age ≥14 days.

Key to Acronyms: ATV = atazanavir; COBI=cobicistat; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV/r = lopinavir/ritonavir; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; RAL = raltegravir; RPV=rilpivirine; RTV = ritonavir; TAF=tenofovir alafenamide

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 1 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
INSTIs In Alphabetical Order		Integrase Inhibitor Class Advantages: • Susceptibility of HIV to a new class of ARVs • Few drug-drug interactions • Well tolerated	Integrase Inhibitor Class Disadvantages: • Limited data on pediatric dosing or safety
	DTG	• Once-daily administration • Can give with food	• Drug interactions with EFV, FPV/r, TPV/r, and rifampin necessitating twice-daily dosing
	EVG	• Once-daily administration • Available as a fixed-dose combination tablet containing EVG/COBI/FTC/ TDF (Stribild) and as a fixed-dose combination tablet containing EVG/COBI/FTC/ TAF (Genvoya)	• COBI has the potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • COBI inhibits tubular secretion of creatinine and may result in increased serum creatinine but with normal glomerular clearance
	RAL	• Can give with food • Available in tablet, chewable tablet and powder formulations	• Potential for rare systemic allergic reaction or hepatitis
NNRTIs In Alphabetical Order		NNRTI Class Advantages: • Long half-life • Less dyslipidemia and fat maldistribution than PIs • PI-sparing • Lower pill burden than PIs for children taking solid formulation; easier to use and adhere to than PI-based regimens	NNRTI Class Disadvantages: • Single mutation can confer resistance, with cross-resistance between EFV and NVP. • Rare but serious and potentially life-threatening cases of skin rash, including SJS, and hepatic toxicity with all NNRTIs (but highest with NVP) • Potential for multiple drug interactions due to metabolism via hepatic enzymes (e.g., CYP3A4)
	EFV	• Once-daily administration • Potent ARV activity • Can give with food (but avoid high-fat meals) • Capsules can be opened and added to food	• Neuropsychiatric AEs (bedtime dosing recommended to reduce CNS effects) • Rash (generally mild) • No commercially available liquid • Limited data on dosing for children aged <3 year • No data on dosing for children aged <3 months • Use with caution in adolescent females of childbearing age
	NVP	• Liquid formulation available • Dosing information for young infants available • Can give with food • Extended-release formulation is available that allows for once-daily dosing in older children	• Reduced virologic efficacy in young infants, regardless of exposure to NVP as part of a peripartum preventive regimen • Higher incidence of rash/HSR than other NNRTIs • Higher rates of serious hepatic toxicity than EFV • Decreased virologic response compared with EFV • Twice dosing necessary in children with BSA <0.58 m^2
	RPV	• Once-daily dosing • Available in a one-pill daily fixed drug combination	• Should not use in patients with HIV viral load >100,000 copies/mL • Low barrier for resistance

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 2 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
PIs In Alphabetical Order		PI Class Advantages: • NNRTI-sparing • Clinical, virologic, and immunologic efficacy are well documented • Resistance to PIs requires multiple mutations • When combined with dual NRTI backbone, targets HIV at two steps of viral replication (viral reverse transcriptase and protease enzymes)	PI Class Disadvantages: • Metabolic complications including dyslipidemia, fat maldistribution, insulin resistance • Potential for multiple drug interactions because of metabolism via hepatic enzymes (e.g., CYP3A4) • Higher pill burden than NRTI- or NNRTI-based regimens for patients taking solid formulations • Poor palatability of liquid preparations, which may affect adherence to treatment regimen • Most PIs require ritonavir boosting resulting in associated drug interactions
	ATV/r	• Once-daily dosing • Powder formulation available • ATV has less effect on TG and total cholesterol levels than other PIs (but RTV boosting may be associated with elevations in these parameters)	• No liquid formulation • Food effect (should be administered with food) • Indirect hyperbilirubinemia is common but asymptomatic • Must be used with caution in patients with pre-existing conduction system defects (can prolong PR interval of ECG) • RTV component associated with large number of drug interactions
	DRV/r	• Can be used once daily in children aged ≥12 years • Liquid formulation available	• Pediatric pill burden high with current tablet dose formulations • Food effect (should be given with food) • Must be given with RTV boosting to achieve adequate plasma concentrations • Contains sulfa moiety. The potential for cross sensitivity between DRV and other drugs in sulfonamide class is unknown • RTV component associated with large number of drug interactions • Can only be used once daily in absence of certain PI-associated resistance mutations
	LPV/r	• LPV only available coformulated with RTV in liquid and tablet formulations • Tablets can be given without regard to food but may be better tolerated when taken with meal or snack	• Poor palatability of liquid formulation (bitter taste), although palatability of combination better than RTV alone • Food effect (liquid formulation should be administered with food) • RTV component associated with large number of drug interactions • Should not be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age ≥14 days • Must be used with caution in patients with preexisting conduction system defects (can prolong PR and QT interval of ECG)

Table 8. Advantages and Disadvantages of Antiretroviral Components Recommended for Initial Therapy in Children[a] (page 3 of 3)

ARV Class	ARV Agent(s)	Advantages	Disadvantages
Dual-NRTI Backbones In Alphabetical Order	ABC **plus** (3TC **or** FTC)	• Palatable liquid formulations • Can give with food • ABC and 3TC are coformulated as a single pill for older/larger patients; ABC, 3TC are also coformulated with DTG for use in adults	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment
	ddI **plus** (3TC **or** FTC)	• Delayed-release capsules of ddI may allow once daily dosing in children aged ≥ 6 years, weighing ≥20 kg, able to swallow pills, and who can receive adult dosing along with once-daily FTC • FTC available as a palatable liquid formulation administered once daily	• Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue (ddI can be co-administered with FTC or 3TC) • Limited pediatric experience using delayed-release ddI capsules in younger children • Pancreatitis, lactic acidosis, neurotoxicity with ddI
	TAF **plus** FTC	• Once-daily dosing • Less tenofovir-associated renal and bone toxicity with TAF compared to TDF in adults	• Only available as a fixed-dose combination tablet consisting of EVG, COBI, FTC, and TAF; RPV, FTC, and TAF; or TAF and FTC for adolescents ≥12 years
	TDF **plus** (3TC **or** FTC) for adolescents, SMR IV or V	• Once-daily dosing for TDF • Resistance is slow to develop • Less mitochondrial toxicity than other NRTIs • Can give with food • TDF and FTC are co-formulated as single pill for older/larger patients • Available as reduced-strength tablets and oral powder for use in younger children	• Limited pediatric experience • Potential bone and renal toxicity, toxicity may be less in postpubertal children • Appropriate dosing is complicated by numerous drug-drug interactions with other ARV agents including ddI, LPV/r, ATV, and TPV
	ZDV **plus** (3TC **or** FTC)	• Extensive pediatric experience • ZDV and 3TC are coformulated as single pill for older/larger patients • Palatable liquid formulations • Can give with food • FTC is available as a palatable liquid formulation administered once daily	• Bone marrow suppression with ZDV • Lipoatrophy with ZDV
	ZDV **plus** ABC	• Palatable liquid formulations • Can give with food	• Risk of ABC HSR; perform HLA-B*5701 screening before initiation of ABC treatment • Bone marrow suppression and lipoatrophy with ZDV
	ZDV **plus** ddI	• Extensive pediatric experience • Delayed-release capsules of ddI may allow SMR dosing of ddI in older children able to swallow pills and who can receive adult doses	• Bone marrow suppression and lipoatrophy with ZDV • Pancreatitis, neurotoxicity with ddI • ddI liquid formulation is less palatable than 3TC or FTC liquid formulation • Food effect (ddI is recommended to be taken 1 hour before or 2 hours after food). Some experts give ddI without regard to food in infants or when adherence is an issue

[a] See Appendix A: Pediatric Antiretroviral Drug Information for more information.

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; ARV = antiretroviral; ATV/r = atazanavir/ritonavir; BSA = body surface area; CNS = central nervous system; COBI = cobicistat; DRV/r = darunavir/ritonavir; ddI = didanosine; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EVG=elvitegravir; FTC = emtricitabine; HSR = hypersensitivity reaction; INSTI = integrase strand transfer inhibitor; LPV/r = lopinavir/ritonavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; PK = pharmacokinetic; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SJS = Stevens-Johnson Syndrome; SMR = sexual maturity rating; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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